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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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For the President of the European Patent Office

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Drains for medical applications

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Title: Drains for medical applications

The invention relates, generally, to medical appliances. More particularly, it relates to tubular shaped devices used as drains or catheters for draining fluids (liquids and/or gases) from antrums or other parts of the human or animal body.

In both human and veterinary medicine, it is often desirable to get access to an antrum in order to discharge pus or other material which may form as a result of inflammatory conditions. This is for instance the case with (chronic) sinusitis or inflammatory conditions in the middle ear.

Chronic sinusitis symptoms can be difficult to treat, in part because treatment may require the coordinated efforts of several specialists to treat all of the aspects of the disease. Chronic sinusitis can be broken down into bacterial chronic sinusitis and non-infectious chronic sinusitis. Both have different medical treatment options. Many people with non-infectious chronic sinusitis respond to topical or oral steroids or nasal washes treatments.

Depending on the severity of the sinusitis, there are several treatments to consider such as antibiotics and sinus surgery. Sinus surgery is generally a last line of defense for doctors to relieve a sinusitis condition. In this type of surgery the natural opening to the sinuses is enlarged. The procedure removes areas of obstruction, with the aim of reinstating the normal flow of mucus.

Unfortunately the new opening or connection between the sinus and the nasal cavity has the tendency to re-narrow (restenose) necessitating a re-intervention. Therefore sinus-nasal stents, drains or cannula's have been developed to further improve the result of the drainage procedure.

US-A-4 737 141 discloses a method to drain the maxillary sinus with a plastic temporary drain, which method is an improvement of the classical treatment with multiple lavages of the antrum.

However, the drawback of the currently available drains is that it is required to remove the drain in due time. Removal of these drains may

damage the new drainage tract causing it to re-occlude, is time-consuming and is unpleasant for the patient.

In a majority of cases the drains according to the state of the art are left in place only for a short period of time before they are removed. However, in some cases it is desirable to leave the drain in place for a longer period of time *e.g.* because the antrum, surrounding tissue or anatomical structure needs more time to heal. Known nasal drainage tubes may be left in place for as long as 6 months or more to drain an antrum.

Leaving these known drains in place for a long period of time may lead to complications. The materials used for known drains (usually plastic) may induce irritation but may also inflict an inflammatory response. Inflammatory responses may lead to the formation of scar tissue, which in it self, may require treatment, especially when this occurs in the natural drainage pathway of an antrum. Furthermore, removal of these devices may damage the surrounding tissue because it surface scrapes and damages the tissue. It is also possible that the tissue grows attached to the device and pulling it free may consequently damage the tissue.

Apart from the application in draining fluids or gases from antrums, drains are also applied to drain fluids from organs or tissue. In surgically operated area's a drain is left behind for several days to drain the tissue fluid. Also drains can be applied directly to organs if the effluent of that organ can not by drained via the natural route. Sometimes drain tubes become blocked or occluded so that they have to be removed or exchanged. Especially when the drain has to be applied for a longer period of time it may become fixed in the body, making removal very difficult or even impossible and not without discomfort and risk for the patient.

Accordingly there is a need for a novel, temporary drain, which drain remains functional in the body or antrum orifice for the duration of the prescribed, clinical appropriate period of time to accomplish the predetermined therapeutic purpose.

It was found that this can be obtained by providing drains made from a biodegradable material. Thus, the present invention relates to a drain suitable for draining a human or animal antrum, characterized in that it comprises a biodegradable material. The biodegradable material is preferably a biodegradable polymer.

A drain is defined herein as a tube, optionally having perforations, which is placed into an (artificial) orifice in the wall of an antrum, an organ or tissue. The function of the drain is to carry fluids (liquids and/or gases). A drain differs from a stent in that stents are used to mechanically support lumen walls (such as the colon or blood vessels) in case of strictures or obstructions. Drains may be flexible if the application so requires. Also, since drains generally do not have to support lumen walls, the resilience may be lower than that of stents.

Also regarding its degradation behavior, the drains of the present invention differ from biodegradable stents. The degradation of biodegradable stents usually starts and continues from the outside towards the inside. In particular when stents are applied in blood vessels, it is very important that no fragments of partially degraded material are released on the inside of the tube, since this could lead to migration of these fragments through the body, which would be hazardous. In the drains according to the present invention, however, the degradation may commence and propagate on the inside towards the outside, optionally under influence of the fluids that are drained. If fragmentation occurs, this generally does not present any problems, since these fragments are transported to locations (such as the environment or the oral cavity) were they can do no harm. The drain of the present invention may be essentially cylindrical (*viz.* having a constant cross-section) or its cross-section may vary in order to suit specific applications, *e.g.* by providing it with a funnel shaped end, as will be described hereinbelow in more detail.

Biodegradable materials such as polymers have been used for many medical applications that require only a temporary presence of a device in the

body. Devices of biodegradable materials are used mainly in tissue recovery and drug delivery. These materials can be used as films, sheets, tubes, plugs, pins, rods, fibres, ligaments, scaffolds, microspheres, membranes, and so forth. These products, which can be solid or porous, can have all kind of shapes. Devices of biodegradable material have been used as an implant or in wound closure, as wound dressings or artificial skin and can be applied in the mucous membrane tissue by insertion via a body orifice *e.g.* for tissue recovery after a surgical procedure or an injury.

Biodegradable materials originating from a natural source have been used in medical applications, for example Type I collagen, hyaluronic acid derivatives and chitosan.

The majority of biocompatible, biodegradable synthetic materials is based on synthetic polyesters made of (mixtures of) cyclic lactones such as glycolide, lactide, caprolactone, para-dioxanone, trimethylenecarbonate and of polyesters made by a condensation reaction of diols and diacids or hydroxyalkanoic acids. These polyesters can be used as such or in combinations with polyethers, polyurethanes, polyamides or with organic or inorganic compounds. A wide range of medical devices have been developed and/or manufactured so far of this type of biomaterials.

European patent application No. 00201189.8 discloses the use of a copolymer of DL-Lactide and ε-caprolactone with a specific composition in the manufacture of a biodegradable nerve guide, which is a flexible, solid tube. A specific monomer composition is required to supply the product with the best performance properties such as mechanical strength, softening temperature and compression modulus.

US-B2-6 423 092 discloses a biodegradable stent for implantation in a body lumen made of two layers of a different biomaterial composition, resulting in a different degradation rate if the inner and outer layer. This type of stent is being developed for replacing permanent stents *e.g.* for treating stenosis of the lumen in urological applications.

In US-A-5 085 629 a bioresorbable ureteral stent made of a terpolymer of lactide, glycolide and caprolactone is disclosed.

The use of a biodegradable tube for draining an antrum is not disclosed before. The materials properties (mechanical, physical and degradation) will be different from those of previously described stents or drainage tubes and will be specific for application of a biodegradable drain. The properties which the drain has to fulfill will be discussed in more detail in the description of the preferred embodiment.

A drain of a biodegradable material will have the advantage that it degrades over time where after it is being resorbed and/or excreted by the body. This has the advantage that no additional intervention is required to remove the device, but also that the complication frequency of the treatment, associated with the removal is reduced. Because the biodegradable drains are similar in design to the biodurable devices, rinsing the antrum, which is desired in some clinical cases, remains possible.

An example of such a biodegradable drain tube could be the drainage of bile form the liver. This is required in patients where the natural bile secretion pathway has become blocked, *e.g.* due to tumor growth or liver necrosis.

The drain can be used until it becomes blocked. A biodegradable drain can be used longer than the biodurable version since the biodurable version has to be removed before they get occluded and fixed in the patient. Instead of removing the biodurable drain with patient risk and discomfort, the biodegradable drain is left in place where it degrades and is being absorbed over time. A new biodegradable drain can be placed to take over the function of the previous one.

The use of bioabsorbable and biodegradable materials for manufacturing temporary medical devices is well known and common practice. They have excellent bio-compatibility characteristics, especially in comparison to the most conventional used biodurable materials. In general, the use of a

biodegradable drain will overcome the potential complications associated with biodurable devices when used for both short and longer periods of time.

The present invention provides a device for draining an antrum which is manufactured of a biodegradable material and which is easily passed from the body or antrum orifice after a specific therapeutic period of time.

The biodegradable drain of the present invention may further be used for draining tear fluid from a nasolacrimal duct.

The biodegradable drain of the present invention can be employed for treating frontal and maxillary sinusitis. Preferably the drain has a distal end to retain the drain in the sinus cavity (anchor). The drain can be inserted through the natural orifice or through an opening made by a surgical procedure. The drain can be introduced *e.g.* by the use of a forceps, a guidewire, a trocar or unsupported by use of its own mechanical properties (stiffness).

Furthermore, the drains of the invention may be used to vent the inner ear with a biodegradable tube.

The present invention provides drains made of biodegradable polymeric materials, which degrade with such a rate giving the surrounding tissue time to heal, maintaining an opening of the antrum and without damaging the surrounding tissue when it degrades. The degradation products of this biocompatible, biodegradable drainage device are cleared either via the digestive channel, the body or antrum orifice or absorbed by the body and metabolized or secreted.

Figure 1 shows a straight biodegradable drain of the present invention. Figure 2 shows an example of a biodegradable frontal sinus drain of the present invention. Figure 3 shows an example of a biodegradable ear vent of the present invention.

The drain according to the present invention, comprises cylindrical tubes (drains) of appropriate sizing (outer diameter: from 2-10 mm, total length of 30-300 mm, wall thickness from 0.2-2.0 mm) for being used in

draining various antrums or organs. As shown in Figure 1 the drain can be a hollow tube of substantial length and diameter for being applied as a nasolacrimal duct to temporarily drain the tear fluid where after the tube degrades and the original nasolacrimal duct takes over its function. Straight tubing is, in general, suitable for draining antrums or organs where fixation in the anatomical location by a special tube design is less critical as in the case of the nasolacrimal duct.

Figure 2 shows a drain which may be used as a frontal sinus drain in accordance with the present invention, supplied with a funnel (6) at one end of the tube. The drain is characterized by a wall thickness (1), an inner diameter (2), an outer tube diameter (7), a tube length (3), a funnel length (4) and funnel diameter (5). The funnel ensures fixation of the tube in the antrum. This funnel shape is much more preferred than conventional shapes employed for this purpose, such as the "split-end" type of anchoring described in US-A-4 737 141. It was found that these conventional anchoring means provide for dead spaces or volumes in which stagnant fluid may collect, which in turn form a source of microbiological activity, which may lead to further complications. According to the present invention it is possible to provide anchoring means, such as the funnel shape depicted in Figure 2, with a smooth and continuous surface, by which these problems can be avoided.

Typically, the tube of Figure 2 may be used for draining the frontal and/or maxillary sinus. The device can be made out of one piece. The size of the funnel may vary from 3–30 mm in inner diameter and 2-20 mm in length. The dimensions of the cylindrical part are related to each other as in the case of the tube of Figure 1.

Another embodiment of a drain of the present invention is seen in Figure 3. A cylindrical tube of a single piece, with two flanges, one on each side. A possible application, but not restricted to this, is the drainage of the middle ear. The tube is intended to vent the middle ear and is placed in the

tympanic membrane. The tube is placed in an artificially made puncture in the membrane.

The dimensions of the drains and relative dimensions of parts of the drain of Fig. 1-3 will depend on a number of factors, including the anatomy of the patient and the type of surgical procedure.

According to the invention the drain is made of a biodegradable material. A biodegradable material may be completely resorbed by the body or may degrade by fragmentation of the material. The fragments are cleared either via the digestive channel or via an antrum orifice.

The biodegradable material can be, but is not preferred, of a natural source based on, but not limited to, collagen, hyaluronic acid and its derivatives, chitin, chitosan, polysaccharides, polypeptides. These materials are not preferred, because they can be contaminated. The contamination can be transferred to the patient treated with the device. Furthermore, properties of natural polymers are more difficult to tune. Also, there may be considerable batch to batch variations in these natural polymers and generally, they possess poorer mechanical properties. Also, they are in general more expensive than synthetic materials.

In a more preferred embodiment, the biodegradable material is a synthetic material such as a polymer. The polymeric material can be a thermoplastic linear polymer or a thermoset polymer obtainable by cross-linking of (pre)polymers. Examples of synthetic biodegradable materials that can be applied for manufacturing the drains of the present invention are based on polyesters, polyhydroxyacids, polylactones, polyetheresters, polycarbonates, polydioxanones, polyanhydrides, polyurethanes, polyester(ether)urethanes, polyurethane urea, polyamides, polyesteramides, poly-orthoesters, polyaminoacids, polyphosphonates and polyphosphazenes. The polymeric material may also be composed of mixtures of above components either as different building blocks of the copolymer or cross-linked polymer or as a blend of two or more (co)polymers. Composites of these polymers with organic and

inorganic compounds (*e.g.* radiopaque fillers) are also possible. In addition, the polymer may be loaded with pharmaceutical components such as antibiotics, anti-inflammatory agents, anaesthetics, proteins and many more. The polymer can be loaded with pharmaceutical components by mixing the components (*e.g.* pure or dissolved in a solvent such as water) with the polymer solution, after which the solvent is evaporated and/or freeze dried. Mixing is performed preferably with a turrax homogenizer.

Evidently, the possibilities are not limited to the above mentioned polymers but also other materials may be used, as long as they are biodegradable and biocompatible and having the desired mechanical, physical and degradation properties. Polymers are however the preferred materials, since they enable the design of drains having the desired properties (such as degradation behaviour and mechanical properties) by selecting the proper synthesis conditions for the polymer.

The preferred biodegradable polymers used for drains according to the present invention, are those based on polyesters, polycarbonates, polyanhydrides, polyurethanes and/or polyamides, *viz.* the preferred biodegradable polymers comprise ester (-C(O)-O-), carbonate (-O-C(O)-O-), anhydride (-C(O)-O-C(O)-), urethane (-NH-C(O)-O-) and/or amide (-NH-C(O-) groups. These polymers degrade by a hydrolysis and/or enzymatic mechanism of the ester, carbonate, anhydride, urethane or amide linkages. The rate of degradation can be regulated by choosing the content and combination of monomers. The polyesters, polycarbonates or polyanhydrides can either be homopolymers or copolymers. The copolymers can be random or can be block – or segmented copolymers in which preferably the copolymer or at least one block or segment is a polyester, polycarbonate or polyanhydride with a glass transition temperature (Tg) equal to or below the body temperature, generally 37 °C. In case the copolymer has a phase separated structure, a first block is based on the polyesters, polycarbonates, polyanhydrides and/or polyurethanes mentioned above. This first block is also referred to as the "soft" block and is

amorphous. The other (second) block or segment forms a hard block such as urethane, amide, or crystalline or high Tg (>37 °C) polyester- or polyanhydride blocks.

The biodegradable polymer can also be combined with hydrophilic polymers, such as polyethers, polyvinylalcohol, polyvinylpyrrolidone or poly(hydroxymethylmethacrylate) (poly-(HEMA)). This means that the above-mentioned (co-)polymers chains are chemically combined with these hydrophilic polymers, *e.g.* by choosing synthesis conditions such that also the hydrophilic polymers are incorporated in the backbone or in the side-chain of the resulting copolymer. The preferred polyether is polyethyleneglycol. Other suitable polyethers are polytetramethyleneoxide (PTMO) and copolymers of *e.g.* polyethyleneglycol and polypropyleneglycol. The preferred molecular weight and amount of the polyethers is dependent on the hydrophilic properties that are demanded by the product. The polyethers can be mixed or can be a pre-polymer in combination with the biodegradable (pre)polymers.

The relative amounts of components must be chosen in such a way that a product with the desired thermal, mechanical, hydrophilic and degradation properties is obtained.

A drain for the above mentioned applications must be flexible, pliable and elastic. These properties can be obtained by using an appropriate processing method. For example, by winding of polymeric fibers into a coiled spring structure or by knitting or weaving of fibers, an open structured tube with above mentioned properties can be obtained, optionally followed by a dip-coating run to close the openings. Preferably, the drain is obtained by dip-coating of a polymer solution on a mandrel or extrusion of a polymer. A solid tube is then obtained, after which perforations or carvings can be made. Drains with elastomeric properties when placed in the body can be achieved by using a material with a softening point (Tg) equal to or below 37 °C. The physical cross-links that are required for these properties can be formed by chain entanglements which are present in an amorphous, high molecular

weight copolymer or, in case of a phase separated copolymer, by crystalline or high Tg segments with a melting or glass transition temperature higher than 37 °C. Drains based on materials with chemical cross-links can be made when the pre-polymer and cross-linking agent are mixed and reacted in a predetermined shape *e.g.* by reacting in a mould or extruding the mixture of reacting components.

It is preferred to make the drain in one piece from a thermoplastic elastomeric polymer by a dip-coating process. In the dip-coating process, a mandrel, having the shape of the drain to be obtained and which thus functions as the template for the drain, is submerged in a solution of the polymer (usually an organic solvent). After the mandrel is removed from the solution, a layer of solution remains adhered to its outer surface. Subsequently the solvent is evaporated. Optionally the procedure may be repeated to obtain drains having a higher wall thickness. Drains with various dimensions can be made in this way, depending on the dimensions of the mandrel. The thickness of the drain can be regulated by the number of dip-cycles. Also, the drain can made by extrusion. In this case, the polymer should be thermally stable, should not contain chemical cross-links and should not have a too high melting temperature or melt viscosity.

A biodegradable drain made of a synthetic polymer is preferably a flexible solid tube (with or without perforations) with an elastic modulus varying from 1-120 MPa. More preferably, and in particular for frontal sinus drains, the elastic modulus is 2-10 MPa. Drains have preferably a tensile strength of more than 2 MPa at an elongation at break of 500-1300 %, more preferably the drains have a tensile strength of more than 5 MPa.

A polymeric material that fulfils all of the criteria will be a copolymer of lactide and ε-caprolactone. The lactide can be L, D or D,L-Lactide. The lactide content is preferably between 51-75%, because there is little or no swelling of the material with this composition. Too much swelling will close the lumen so that drainage is prohibited. Most preferably, the lactide content is

62-69% and having a L/D ratio of 85/15. In case a racemic lactide is used, the molecular weight of the copolymer must be high enough to give the tube elastic properties. The physical cross-links that give the material its elastic properties are caused by chain entanglements that can only be present if the molecular weight is high enough. An intrinsic viscosity (which is a measure for Mw) of at least 3 dl/g is very suitable in that case. In case an isomeric lactide or a lactide with an L/D ratio away from unity is used, physical cross-links can be obtained by poly-lactide sequences. A lower molecular weight is acceptable. In general, the intrinsic viscosity may vary from 1-6 dl/g. The time until the drain starts to loose its mechanical properties will be dependent on the starting molecular weight. A drain of a lactide-caprolactone copolymer material will keep its performing properties for about 2-12 weeks.

Another preferred embodiment is the use of segmented or block-copolymers comprising polyesters, polyester-carbonates or polyanhydrides. Preferably, these polymers have at least one Tg and one melting temperature or two separate Tg's within a copolymer, the first transition being lower than 37 °C, the second transition being higher than 37 °C. Also segmented or block copolymers with only one Tg of mixed phases are possible. Examples of the amorphous soft phase forming pre-polymers are those based on cyclic and/or non-cylic monomers such as lactide, glycolide, ε-caprolactone, δ-valerolactone, trimethylenecarbonate, tetramethylenecarbonate, 1,5-dioxepane-2-one, para-dioxanone and/or hydoxyalkanoic acid. The second phase may be formed by pre-polymers comprising poly-caprolactone, poly-valerolactone, poly-lactide, poly(lactide-glycolide), poly-*para*-dioxanone, poly(hydroxybutyricacid), polysebacic acid or poly(dodecanedioicanhydride) and combinations thereof.

A suitable phase separated copolymer of this type is a DL-lactide-caprolactone copolymer with a lactide content of 20-40%. In this case, the ε-caprolactone content is high enough to crystallize. The amount of crystallization depends on the ε-caprolactone content and on the distribution of monomers. The monomers can be randomly distributed but preferably, the

polymer is a segmented or block-copolymer with crystalline poly-caprolactone hard segments and amorphous poly(lactide-ε-caprolactone) soft segments. The general structure of these phase separated copolymers is $[-A-B]_n$ or ABA. n denotes the number of repeat units of -A-B- in case the segments A and B are alternating. $[-A-B-]_r$ is the notation for a multi-block segmented copolymer in which the segments A and B are randomly distributed and the ratio A/B is not necessarily equal to one. ABA is a triblock copolymer of segments A and B. A and B can be both the hard phase and soft phase forming segment, but can not be the same in one copolymer. The pre-polymer segments are preferably linked by an aliphatic diisocyanate, more preferably 1,4-butanediisocyanate. The crystallization of poly-caprolactone segments will give a copolymer with a phase separated morphology, which will result in thermoplastic elastomeric properties.

By using this synthesis route the molecular sequence of a copolymer can be controlled as desired for a particular application. A drain made of this material may keep its performing properties for several months, depending on its composition. Materials with better mechanical and thermal properties than of random copolymers of ($^{50}/_{50}$) DL lactide and ε-caprolactone or lactide-caprolactone copolymers with a major lactide content, i.e. more than 50%, may be obtained. An elastic modulus of more than 10 MPa can be obtained and a tensile strength of more than 5 MPa.

Another preferred embodiment is the use of biodegradable poly-urethanes for drains. The polymer is build of alternating polyester and/or polycarbonate soft segments and urethane hard segments, giving a phase separated structure. Polymers with very good mechanical properties can thus be obtained. Preferably, the urethane hard segments have a uniform block length which can be obtained by different chain-extending methods. A polymer with the highest degree of phase separation may be obtained by chain-extending the pre-polymer (hydroxyl terminated in case the initiator is a diol) with a diisocyanate chain-extender. Diisocyanate chain-extenders that are

suitable for obtaining polymers with uniform hard segments and with sufficient mechanical properties are e.g diisocyanate end-capped diol components, obtained by the reaction product of the diol with two equivalents of the diisocyanate. The diisocyanate is preferably 1,4-butanediisocyanate; the diol is preferably a linear aliphatic diol or a (poly)ethylene glycol with general structure HO-(CH_2)n-OH with n = 2-8 or HO-(CH_2CH_2-O)n-H with n = 1-8, respectively. Even more preferably, the diol is a reaction product of two moles of these linear aliphatic diols or (poly)ethylene glycols with a diisocyanate, preferably 1,4-butanediisocyanate (obtainable by reacting the diisocyanate with an excess of the diol).

The phase separated segmented polyurethane can also be obtained by a method in which the di-hydroxy terminated pre-polymer is reacted with an excess of a diisocyanate, resulting in an isocyanate end-capped pre-polymer. Subsequently chain-extending with a diol compound or a reaction product of two equivalents of the diol with a diisocyanate will give a phase separated polyurethane with uniform block length. As diol compounds the above-mentioned linear aliphatic diol or (poly)ethylene glycol compounds may be used and preferably the above-mentioned reaction product of these diols with a diisocyanate. are used. The degree of phase separation may in some cases be somewhat less than obtained with the first given chain-extending method. This is the result of trans-esterification reactions of labile ester groups. The polyester soft segment is a pre-polymer build of (mixtures of) monomers such as lactide (L,D or L/D), glycolide, ε-caprolactone, δ-valerolactone, trimethylene carbonate , tetramethylenecarbonate, 1,5-dioxepane-2-one or para-dioxanone. The pre-polymer is preferably 50/50 (DL-lactide -ε-caprolactone) with a molecular weight of 2000 obtained by a ring opening polymerisation initiated by a diol compound. The rate of degradation will depend on the initial molecular weight (measured by the intrinsic viscosity) and the type of pre-polymer. Optionally, polyethers are added to the polyester or polycarbonate pre-polymers, either as an initiator or as a pre-polymer. The preferred

polyether is a polyethyleneglycol. Phase separated polyurethanes with molecular weights of the pre-polymer of 2000 may have an initial elastic modulus varying from 30-120 MPa and a tensile strength of 10-45 MPa. The elongation at break varies from 500-1200 %.

The mechanical and degradation properties of the drains can easily be tuned by using a physical blend of suitable polymers. For example, a polyurethane can be blended with a copolymer giving a material with intermediate properties of the components. Preferably, the soft segment pre-polymer of the polyurethane is compatible (miscible) with the copolymer. A DL-lactide-ε-caprolactone based polyurethane is very well miscible with a lactide-caprolactone copolymer, due to the miscibility of the copolymer and pre-polymer soft segment.

Drains that need to be kept in place for a much longer period of time before disintegrating, such as drains for the mid ear which may require to be put in place for a time of 6 to 9 months, are preferably made of polyesters, polycarbonates, polyurethanes, poly-anhydrides, polyamides or other polymers with slowly hydrolysable groups. The polyester or polycarbonate segments need to be build of slowly degrading monomers such as ε-caprolactone, δ-valerolactone. trimethylenecarbonate, tetramethylenecarbonate, para-dioxanone. Optionally, polyethers can be added.

Examples

Analysis Methods and Characterization of copolymers:

The following analysis methods were used in all examples, unless indicated otherwise.

The intrinsic viscosity was measured in chloroform at 25 °C using an Ubbelohde viscometer (according to ISO standard 1628-1).

The value for the intrinsic viscosity ([η]) thus obtained (expressed in dl/g) is converted into the weight average molecular weight (Mw) by using the Mark-Houwink expression: $[\eta] = KM_w^a$, wherein K and a are polymer specific

parameters. The K and a values that were calculated for copolymers with 45-55% lactide have also been used for copolymers with higher lactide contents. In a similar way, the number average molecular weight, Mn, is calculated. This relation is used only for lactide-caprolactone copolymers.

Monomer conversion, monomer distribution (average sequence length, $\bar{L}_{Lac}$ and $\bar{L}_{Cap}$) and copolymer composition were determined using ^{1}H-NMR at 300 MHz in solutions in deuterated chloroform.

Thermal properties were determined using a TA Instruments-Q1000 MDSC,5-10 mg samples being heated at a rate of 10 °C per minute, cooled down at a rate of 20 °C per minute and heated again at a rate of 10 °C per minute.

Purification and/or drying of monomers and glassware is according to previously published methods and is sufficient to obtain polymers with the desired properties.

Determination of mechanical properties of drains:

The stress strain behavior of straight tubular drains was determined with an Instron 4301 tensile tester. The tubes were measured at room temperature at a crosshead speed of 10 mm/minute. The ultimate tensile strength, the elongation at break and the initial modulus were determined from these measurements.

Example 1: Synthesis of 65:35 (85/15)L/D Lactide-ε-caprolactone

DL-Lactide and L-Lactide (ratio 70:30) (Purac, the Netherlands) were introduced into the reaction vessel under nitrogen atmosphere and were dried in vacuum at 45 °C for at least 8 hours. ε-caprolactone (Acros, Belgium) is dried over CaH_2 and distilled under reduced pressure in a nitrogen atmosphere.

Glass ampoules are covered inside with a teflon sheet (fluortec) and are dried in an oven during one night. ε-Caprolactone was added to the lactide in the vessel in a monomer ratio 62/38 mol/mol (lactide/ε-caprolactone).The catalyst was added in an amount of 1 x 10^{-4} mole of catalyst per mole of monomer. After 20 minutes of homogenisation at 120 °C the mixture was poured into the glass ampoules under nitrogen flow, after which the ampoules were closed with a stop. The ampoules were placed at 110 °C for 312 hours (13 days). The intrinsic viscosity was 6.2 dl/g. The monomer conversion was 95%.The lactide content in the polymer (calculated by NMR) was 65%. The glass transition temperature was 14.6 °C.

Example 2: DL-Lactide-ε-caprolactone prepolymer (Mn=2000)

The pre-polymer was synthesized by ring opening polymerization of ε-caprolactone and ($^{50}/_{50}$) DL lactide in a 50/50 (mol/mol) ratio using 1,4-butanediol as initiator and stannous octoate as catalyst. After reaction at 130°C for 5 days, ^{1}H-NMR shows complete monomer conversion.

Example 3: ε-Caprolactone prepolymer (Mn=2000, 3000 and 4000)

The pre-polymer was synthesized by ring opening polymerization of ε-caprolactone using the appropriate amount of 1,4-butanediol as initiator and stannous octoate as catalyst. After reaction at 130°C for 5 days, ^{1}H-NMR shows complete monomer conversion.

Example 4: Synthesis of segmented co-polyesters with randomly distributed segments: P(CL-DLLA): poly(caprolactone-DL-lactide)

Poly-caprolactone pre-polymers with Mn = 2000, 3000 or 4000 of Example 3 and DL-lactide-ε-caprolactone (50:50) pre-polymer of Example 2 are weighted in the appropriate amounts into a glass ampoule supplied with

nitrogen inlet and a mechanical stirrer. 1 equivalent of 1,4-butanediisocyanate (Bayer, distilled at reduced pressure) is added. The contents of the ampoule are quickly heated to 65 °C and then stirred mechanically for 15 minutes. As the mixture becomes viscous, the temperature is increased to 80 °C. Stirring is stopped when the mixture becomes too viscous and the heating is continued for. a maximum of 24 hours.

De ampoule is cooled to room temperature and the contents are isolated by dissolving the polymer in chloroform. The solution is filtered and poured into a petri-dish. The solvent is evaporated and after that the polymer film is dried in a vacuum oven at 40 °C. In another method, the polymer solution is precipitated in ethanol or other suitable organic solvent, the polymer isolated and dried.

Polymer composition is determined by ^{1}H-NMR. The intrinsic viscosity varies from 1-4 dl/g. The glass transition temperatures of the copolymers vary from –14 °C to –27 °C; the melting temperatures of the crystalline phase lies between 39 °C and 60 °C, Generally, the higher the caprolactone content and caprolactone pre-polymer length, the higher the melting temperature and energy. In Table 1 the thermal properties of a few segmented polyesters are shown. The intrinsic viscosities of these specific copolymers lie between 1.2 and 2 dl/g.

Example 5: Synthesis of (50/50) (DL-lactide-ε-caprolactone) based polyurethane with BDI-BDO-BDI-BDO-BDI hard segment.

A pre-polymer was prepared according to the method of Example 2. The BDO-BDI-BDO chain-extender was prepared according to the method given in international application PCT/NL99/00352 and was subsequently purified, such that a purity of 98% was obtained.. The melting point of the chain-extender was 97°C.

In the first step of the polyurethane synthesis, the hydroxyl terminated pre-polymer is be end-capped with a 5 to 6 fold excess of 1,4-

butanediisocyanate under mechanical stirring. After reaction at 60°C for 4 hours the excess BDI was removed by distillation under reduced pressure.

In the next step of the polymerization, the macrodiisocyanate is chain extended at 65 °C with the BDO-BDI-BDO chain extender using 1,4-dioxane as solvent (25 % w/w). The chain-extender is added in small portions to the well stirred pre-polymer solution. When the solution becomes more viscous, the mixture is diluted with small amounts of dioxane. When the viscosity is not increased anymore, the solution is diluted with dioxane to the desired concentration. The polymer solution can be frozen after which it is freeze dried, it can be precipitated in water or organic solvents or it can be concentrated by evaporation and dried in vacuum. The obtained polyurethane can be processed into a drain according to the method of Example 6.

Example 6: Preparation of drains according to Fig. 1, 2 and 3.

General method:

Drains were prepared of a polymer solution in chloroform or another organic solvent by dip-coating a straight tubular shaped mandrel or a mandrel with a funnel shape at one end with this solution, giving drains with the dimensions and shape of those of Figures 1 and 2, respectively. After dipping, the mandrel was placed horizontally and the solvent was allowed to evaporate during 5 minutes while rotating. This procedure was repeated until the desired wall thickness was obtained. The mandrel with the copolymer layer was placed first in ethanol and after that in distilled water. The tubes were removed from the mandrel and were cut into the appropriate size. They were placed in ethanol, followed by vacuum drying at 40°C in order to remove any monomer- and low molecular weight residues and organic solvents. Tubes of the Example of figure 3 are obtained by carving the appropriate amount of material from the tube.

Example 7: Preparation of a drain of 65:35 (85/15)L/D Lactide-ε-caprolactone copolymer.

Drains of a copolymer of Example 1 were prepared according to the general method of Example 6. Mechanical properties of a 30mm straight tube (without the funnel) part were measured: the initial modulus is 2.9 MPa, the stress at 400% strain is 3.3 MPa, the stress at break is 20 MPa and the strain at break is 750%.

Example 8: Preparation of drains from segmented polyesters.

Drains of multi-block segmented copolymers of Example 4 (polyesters build of poly-caprolactone and poly-(50/50)lactide-ε-caprolactone prepolymers with various ε-caprolactone/lactide ratios and with different pre-polymer lengths) were prepared according to the general method of Example 6. The thermal- and mechanical properties of tubes with different composition are measured. The results are presented in Table 1 and 2, respectively:

Table 1: ***Thermal properties of different phase separated poly(DL-lactide-ε-caprolactone prepolymers.***

% PCL prepolymer	Tg (°C)	Tm (°C)	ΔH (J/g)
33 (Mn=3000)	-16.8	49.0	26.7
40 (Mn=3000)	-17.1	57.7	32.1
50 (Mn = 2000)	-23.1	53.3	27.1

Table 2: ***Mechanical properties of different phase separated poly(DL-lactide-ε-caprolactone prepolymers.***

% PCL prepolymer	Modulus (MPa)	Elongation at break (%)	Stress at break (MPa)
33 (Mn=3000)	19.5	1220	15.1
40 (Mn=3000)	42.1	1330	13.4
50 (Mn = 2000)	31.1	860	8.3

Example 9: Preparation of drains of segmented polyurethanes.

Drains of a polyurethane of Example 5 were prepared according to the general method of Example 6. Mechanical properties of a 30mm straight tube (without the funnel) part were measured: the initial modulus is 35 MPa, the stress at 400% strain is 16 MPa, the stress at break is 41 MPa and the strain at break is 1000 %.

Example 10: Preparation of a drain of 68:32 (85/15)L/D Lactide-ε-caprolactone copolymer and DL-lactide-ε-caprolactone based polyurethane

Drains of a blend of a 68:32 (85/15) L/D-Lactide-caprolactone copolymer and a polyurethane of Example 5 were prepared according to the general method of Example 6. A 50:50 (w/w) mixture of the polymers is dissolved in chloroform. Mechanical properties of a 30mm straight tube (without the funnel) part were measured: the initial modulus is 10 MPa, the stress at 400% strain is 6.7 MPa, the stress at break is 26 MPa and the strain at break is 990%.

Claims

1. Drain suitable for draining a human or animal antrum, organ or tissue, characterized in that it comprises a biocompatible, biodegradable material, preferably a biodegradable polymer.

2. Drain according to claim 1, which essentially entirely consist of a synthetic biodegradable polymer.

3. Drain according to any of the previous claims, wherein the polymer has at least one softening point (glass transition temperature) of at most 37 °C.

4. Drain according to any of the previous claims, wherein the biodegradable polymer comprises a polyester, polycarbonate, polyester-carbonate, polyanhydride, polyurethane and/or polyamide which are optionally combined with polyether groups.

5. Drain according to claim 4, wherein:

- the polyester is selected from lactide polyester, ε-caprolactone polyester, or copolymers thereof; and/or
- the polyether is selected from polyethyleneglycol, polypropyleneglycol, copolymers thereof and polytetramethyleneoxide (PTMO).

6. Drain according to claim 5, wherein the polyester is a random DL-Lactide-ε-caprolactone copolyester, preferably having a lactide content of 20-75 mol %, more preferably 55-70 mol%, most preferably 62-69 mol%.

7. Drain according to claim 6, wherein the fraction of the L-enantiomer or the D-enantiomer of the lactide is from 65-95mol%, preferably from 70-90 mol%, more preferably about 85 mol%.

8. Drain according to claim 4, wherein the polyester, polyester-carbonate and/or polyanhydride is a segmented or block copolymer with randomly or alternating segments or blocks and consisting of at least two blocks with different composition.

9. Drain according to claim 8, wherein the segments or blocks are phase separated hard and soft segments, characterized by at least two phase transitions, one of them being a glass transition temperature lower than 37 °C, the other a glass transition temperature or melting temperature higher than 37 °C.

10. Drain according to claim 8 or 9, wherein the segments or blocks forming the low temperature transition phase are composed of pre-polymers of (mixtures of) cylic or non-cylic monomers lactide, glycolide, ε-caprolactone, δ-valerolactone, trimethylenecarbonate, tetramethylenecarbonate, 1,5-dioxepane-2-one, para-dioxanone and/or hydroxyalkanoicacid.

11. Drains according to claim 8-10, wherein the copolymer or pre-polymers are obtained by a ring opening polymerisation initiated by a diol or di-acid compound.

12. Drains according to claim 8-11, wherein the pre-polymers forming the segments are linked by a difunctional aliphatic compound, preferably a diisocyanate, more preferably 1,4-butanediisocyanate.

13. Drain according to claims 8-12, wherein the hard segment or block is formed by (combinations of) poly-caprolactone, poly-valerolactone, poly-lactide, poly(lactide-glycolide), poly-*para*-dioxanone, poly(hydroxybutyricacid), polysebacic acid or poly(dodecanedioicanhydride) pre-polymers.

14. Drain according to claim 4, wherein the biodegradable polymer comprises a polyurethane, which biodegradable polymer is a phase separated copolymer with a polyester, polyester-carbonate and/or polycarbonate soft segments and urethane hard segments with uniform block length.

15. Drain according to claim 14, wherein the polyurethane is formed by diisocyanate linked pre-polymer and diol components having the formula [-A-B-C-B-]n, wherein A denotes the pre-polymer moiety, B denotes the diisocyanate moiety, C denotes the diol moiety, having a uniform block length; and n represents an integer larger than 1.

16. Drain according to claim 15, wherein the pre-polymer is formed by ring opening polymerisation initiated by a diol or polyethyleneglycol compound of the cyclic monomers lactide, glycolide, ε-caprolactone, δ-valerolactone, trimethylenecarbonate, tetramethylenecarbonate, 1,5-dioxepane-2-one and/or para-dioxanone

17. Drain according to claim 15 or 16,wherein the diisocyanate is 1,4-butanediisocyanate.

18. Drain according to 15-17, wherein the diol component is a linear aliphatic diol (X) with general structure HO-(CH_2)n-OH with n = 2-8 or HO-(CH_2CH_2-O-CH_2CH_2)n-OH with n = 2-8 or the diol (XYX) is a reaction product of two moles of the diol (X) with said diisocyanate.

19. Drain according to claim 14-18, wherein the polyester is a poly(DL-lactide-ε-caprolactone) and the diol compound is the reaction product of two moles of 1,4-butanediol and one mole of 1,4-butanediisocyanate.

20. Drain according to claim 14-18, wherein the polyester is a poly(DL-lactide-ε-caprolactone) and the diol compound is the reaction product of two moles of diethyleneglycol and one mole of 1,4-butanediisocyanate.

21. Drain according to claim 14-20, wherein the soft segment is a combination of a pre-polymer with a polyether pre-polymer, preferably a polyethyleneglycol.

22. Drain according to any of the previous claims, wherein the polymer comprises a polyurethane and a polyester, polyestercarbonate or a polycarbonate, obtainable by solution blending.

23. Drain according to claim 22, wherein the polyurethane is based on a DL-lactide-ε-caprolactone soft segment pre-polymer and the polyester is a poly(DL- lactide-ε-caprolactone) copolymer.

24. Drain according to any of the previous claims, wherein said polymer is loaded with radiopaque fillers and/or pharmaceutical components such as antibiotics, anti-inflammatory agents, peptides and proteins.

25. Drain according to any of the previous claims, which is provided with perforations.

26. Nasal drain according to any of the previous claims.

27. Drain, particularly a nasal drain, according to any of the previous claims, having a wall thickness of 0.2-2.0 mm.

28. Drain according to any of the previous claims, having a total length of 30-300 mm.

29. Drain according to any of the previous claims, having an outer diameter of 2-10 mm.

30. Drain according to any of the previous claims, comprising a funnel shaped element on at least one end.

31. Drain according to claim 11, having a funnel length of 2-20 mm and preferably a funnel diameter of 3-30 mm.

32. Drain according to any of the previous claims, which is obtainable by dip-coating of a polymer solution on a mandrel or extrusion of a polymer.

33. Method for treating a disorder associated with dysfunction of natural drainage of body fluids from an antrum, comprising providing an orifice in a wall of said antrum and introducing a drain according to any of the previous claims in said orifice, such that said antrum is connected with the environment, after which said drain degrades over time and degradation products of said drain are cleared through the digestive channel and/or said antrum orifice and/or absorbed and subsequently metabolized and/or secreted by the body.

34. Method according to claim 33, wherein said disorder is selected from (chronic) sinusitis, inflammation of the middle ear, liver disorders, tear duct disorder, surgical wound drainage, and thoracic disorder.

35. Use of a drain according to any of the claims 1-32 in the preparation of a medicament for the treatment of a disorder as defined in claims 33 or 34.

Title: Drains for medical applications

Abstract

The invention relates, generally, to medical appliances. More particularly, it relates to tubular shaped devices used as drains or catheters for draining fluids (liquids and/or gases) from antrums or other parts of the human or animal body. According to the present invention a drain is provided, which is suitable for draining a human or animal antrum, which drain comprises a biodegradable material, preferably a biodegradable polymer.

Fig. 1

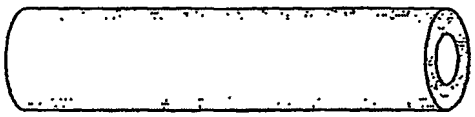

Fig. 2A

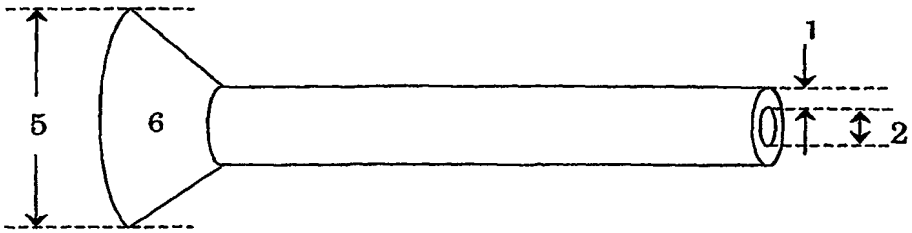

Fig. 2B

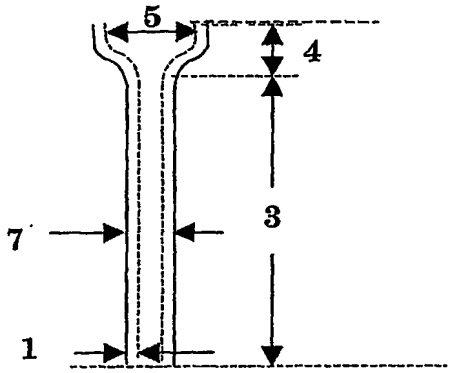

Fig. 3